The restriction requirement

The claims of the application were restricted into seven groups defined by the "insulin-receptor activating compound that is not insulin" of claim 1; and applicants elected Group I and the compound of claim 18 for examination, so that the claims under examination are claims 1 and 2 (in part), 3-5, 11-17 (in part), and 18 (claim 20, while being within Group I, does not read on the elected species).

Applicants note however that claims 1 and 2 are linking claims linking each of the seven groups (drawn to a method of treating a metabolic disorder in a person induced by treatment with an HIV protease inhibitor using an insulin receptor-activating compound), and that claims 12-17 are also linking claims (drawn to a method of treating a metabolic disorder in a person induced by treatment with an HIV protease inhibitor using an insulin receptor-activating compound and another active ingredient: in claim 17 the other active ingredient is a compound from claims 3-11).

The Examiner is respectfully reminded that in the event that the elected subject matter is considered allowable, the Examiner must extend the examination to the non-elected subject matter of the linking claims, for the Federal Circuit has clearly held that it is improper to refuse to examine the entirety of a claim.

The 35 USC 112, ¶2 rejection

Claims 3-5 were rejected under 35 USC 112, ¶2 for indefiniteness for lack of clarity in the definition of the substituent Y. Claim 3 has been amended to limit Y to "alkyl, substituted alkyl, cyano, halo, nitro, $-SR^9$, $-OR^9$, or $-NR^9_2$, where each R^9 is independently hydrogen, lower alkyl, or substituted lower alkyl", a definition which is in compliance with 35 USC 112, ¶2, and which finds support in the application. Claims 4 and 5, dependent on claim 3, now incorporate that same definition.

Withdrawal of the rejection is respectfully requested.

The obviousness-type double patenting rejection

The claims under examination (claims 1-2 in part, 3-5, 12-17 in part, and 18) were rejected for obviousness-type double patenting over claims 29-33 of US Patent No. 6,458,998, which disclose methods of stimulating the kinase activity of the insulin receptor, activating the insulin receptor, stimulating the uptake of glucose into cells displaying the insulin receptor, and treating a disease state in a mammal selected from hyperglycemia, type I diabetes, an type II diabetes by contacting the receptor or cells, or administering to the mammal, a compound of the formula claimed in claim 1 of that patent (compound scope equivalent to claim 3 of this application). The Examiner reasons that the claims are not patentably distinct because they each teach methods of treating hyperglycemia, diabetes, and insulin resistance by employing the same compounds. This rejection is respectfully traversed.

The Examiner reasons that a person of ordinary skill in the art would be motivated to employ the compounds of this application (and in the patent) for the method of treating these disease states regardless of the cause or etiology of the disease, because such a person would reasonably expect the compounds to possess the same pharmacological properties regardless of the etiology of the diseases. Applicants respectfully disagree.

It is undisputed that US Patent No. 6,458,998 discloses that its compounds are insulin receptor kinase activators and that they are useful in the treatment of hyperglycemia, diabetes, and insulin resistance.

However, what is not disclosed in that patent is that the metabolic disorders seen in persons treated with HIV protease inhibitors either have the same biological cause or mechanism as the disease known as diabetes or the symptoms of hyperglycemia, hypertriglyceridemia, and insulin resistance (by which I mean the disease or symptoms seen in persons who have never been treated with HIV protease inhibitors), or that an agent that treats diabetes would also be useful in the treatment of the metabolic disorders seen in persons treated with HIV protease inhibitors.

The Examiner has simply asserted that "one of ordinary skill in the art would have been motivated ... *regardless of the cause/etiology of these diseases.*" (emphasis added). But the Examiner has provided no basis for that statement: it is simply an unsupported assertion without any basis given in the record in this application to date.

In fact, if one looks at the record, including the documents cited in the application and IDSs, there is no statement that IRK activators would be useful in the treatment of the metabolic disorders associated with HIV protease inhibitor treatment. And, while the Saint-Marc article from 1999 suggests that metformin (a biguanide) has reduces visceral adiposity and decreases the plasma insulin response to oral glucose, the Horn et al. article from December 2001 states that while a US study of metformin had been positive, "Unfortunately, metformin failed to pan out as a therapy for either HIV-associated insulin resistance or lipodystrophy in a second randomized, placebo-controlled trial conducted in Barcelona." (page 30, bottom of center column). It also states that, in discussing the glitazones (insulin-sensitizing agents of the thiazolidinedione class, which are PPAR-γ activators), "Unfortunately, the results of two small studies presented in Athens suggest there is little to be excited about." Thus, as of the filing date of this application, metformin, a biguanide antidiabetic, had demonstrated ambiguous results, and pioglitazone and rosiglitazone, two thiazolidinedione antidiabetics, had also demonstrated ambiguous or not statistically significant results.

A January 2003 article in *AIDS ALERT* suggests the use of metformin or a thiazolidinedione [pioglitazone, rosiglitazone, and troglitazone are examples of such drugs], or perhaps even an oral sufonylurea [glipizide is an example of such a drug], a meglitinide, or insulin may be appropriate; but an article in the February 2003 issue of *Southern Medical News*, referring to treatment with pioglitazone and rosiglitazone (troglitazone having been withdrawn for toxicity reasons) says that "Whether similar results (improvements in lipid profile in diabetic patients) will be observed in patients with PI-associated dyslipidemia remains unknown." (page 186, about half-way down the right-hand column).

Applicants submit that, as of the filing date of this application and as of the filing date of the provisional application from which this application claims priority, there was no expectation by persons of ordinary skill in the art that IRK activators would prove useful in the treatment of the metabolic disorders associated with HIV protease inhibitor therapy, and that the Examiner's assertion that "one of ordinary skill in the art would have been motivated ... *regardless of the cause/etiology of these diseases*" is unsupported and incorrect. If the Examiner wishes to maintain this assertion, she is respectfully requested to provide evidence in support.

Applicants therefore respectfully submit that the claims under examination (claims 1-2 in part, 3-5, 12-17 in part, and 18) are not obvious over claims 29-33 of US Patent No. 6,458,998, and withdrawal of the obviousness-type double patenting rejection is requested.

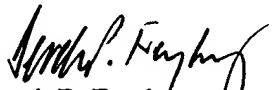
Conclusion

For the reasons given above, Applicants submit that the amended claims are definite under 35 USC 112, ¶2, and are not unpatentable for obviousness-type double patenting over claims 29-33 of US Patent No. 6,458,998. Re-examination, including examination of the linking and non-elected claims, and allowance of the claims are respectfully requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement, listing one new reference from the ISR on the corresponding International Application, is enclosed. In the Response filed September 18, 2002 to the restriction requirement made in this application, Applicants cited two documents on a Form PTO-1449 substitute and provided copies; but a copy of the 1449 was not included with the present Office Action. Applicants request that a copy be included with the next Office Action in this application, together with a copy of the 1449 from the present Supplemental IDS.

Respectfully submitted,



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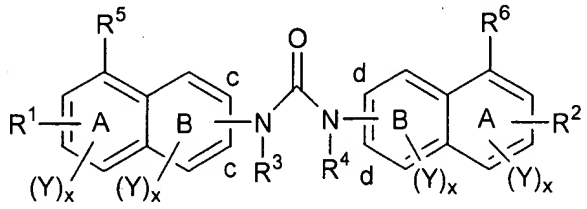
Claim 3 as amended (insertions in bold, deletions in strikethrough)

3. (Amended) The method of claim 1, where the insulin receptor-activating compound is a compound of Formula I



Formula I

wherein:

R^1 and R^2 are substituents on the A ring and are, independently, $-SO_2NR^7{}_2$, $-C(O)NR^7{}_2$, $-NR^7SO_2R^7$, $-NR^7C(O)R^7$, $-SO_2OR^7$, $-C(O)OR^7$, $-OSO_2R^7$, or $-OC(O)R^7$,

R^3 and R^4 are, independently, hydrogen or lower alkyl, or R^3 and R^4 together are $-(CH_2)_2-$, $-(CH_2)_3-$, or $-(CH_2)_4-$,

R^5 and R^6 are, independently, hydrogen, lower alkyl, substituted lower alkyl, cyano, halo, nitro, $-SR^8$, $-C(O)R^8$, $-SO_2OR^8$, $-OSO_2R^8$, $-SO_2NR^8{}_2$, $-NR^8SO_2R^8$, $-OC(O)R^8$, $-C(O)OR^8$, $-C(O)NR^8{}_2$, $-NR^8C(O)R^8$, $-OR^8$, or $-NR^8{}_2$,

each R^7 and R^8 is, independently, hydrogen, lower alkyl, substituted lower alkyl, aryl, substituted aryl, aryl(lower)alkyl, substituted aryl(lower)alkyl, heteroaryl(lower)alkyl, substituted heteroaryl-(lower)alkyl, heterocyclyl, substituted heterocyclyl, heteroaryl, or substituted heteroaryl,

each Y is**, independently, alkyl, substituted alkyl, cyano, halo, nitro, $-SR^9$, $-OR^9$, or $-NR^9{}_2$, where each R^9 is independently hydrogen, lower alkyl, or substituted lower alkyl** ~~a non-interfering substituent~~,

each x is, independently, 0, 1 or 2, and

the urea linker connects a carbon which is designated c with a carbon which is designated d,

or a pharmaceutically acceptable salt thereof, optionally in the form of a single stereoisomer or mixture of stereoisomers thereof.